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Emulgel - A Novel Advance for Skin Disease

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Abstract

A topically applied drug delivery system is used for the direct approach of drugs into the general circulation of the skin. There are many dosage forms to treat dermatological diseases. In that emulgels are recent attention to the scientist, because it has features of both gel and emulsion control release drug delivery system. When gel and emulsion get homogenized together that term is mentioned as emulgel. It is incorporated as a current novel drug delivery system used for topical drug delivery. Emulgels have dual control release mechanism because of the combined features of gel and emulsion. These are either oil-in-water or water-in-oil systems that form a gel-like structure using a polymer called gelling agents. Mixing of gel into emulsion leads to the stable formulation. This novel advance is used for the broad range of active pharmaceutical ingredient molecules mostly for the hydrophobic drug which has less solubility in water. Due to its greaseless texture, it has good patient compliance. Mostly, analgesic and antifungal drugs were introduced into emulgel formulation.

Keywords: Control release mechanism, Emulgel, Gelling agents, Hydrophobic drug, Topical drug delivery system

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Introduction

Since ancient times, human beings have been experiencing several types of diseases affecting their well-being and prosperity. The need to cure these diseases has driven scientific research and the development of various medications, drugs, and delivery systems. Various routes of administration are used to achieve a therapeutic response after taking a drug required to treat an illness. The method of administration is influenced by the type and severity of the disease. For skin disorders, topical administration is generally preferred. To obtain the localizing effect of a drug, a topical application system intended a formulation containing an extensive variety of drug molecules directly to the skin.[1] Taking medication topically is the easiest and simplest way to deliver medicines to numerous parts of the body, such as the ophthalmic, rectal, vaginal, and skin. They might be applied to healthy and diseased skin as an extended variety of cosmetic and dermatological preparations. Topically, administered drugs are introduced to have an immediate or systemic effect on the patient.[2] Topical drug delivery has a number of advantages, including the potential to deliver drugs particularly to the targeted site, excluding gastrointestinal incompatibility, and avoiding metabolic degradation a lot of over topical delivery increases bioavailability by avoiding first-pass effect by the liver and by providing continuous delivery for a distant future.[3] Topically applied dosage forms include Gel, Emulgel, Ointment, Creams, etc. As per USP Gels are described as a semisolid formulation composed of inorganic molecules embedded in a liquid enclosing and interpenetrating each other. Although topical gels have numerous benefits such as easy to apply, less greasiness, and easy removal, they are not effective in delivering hydrophobic drugs.[4] The most critical problem with topically applied gel is the dissolution and diffusion of hydrophobic drugs and the penetration of hydrophilic drugs through the stratum corneum. To compensate for this lacking, the emulgel is prepared to allow a hydrophobic therapeutic molecule to gain the benefits of gels. Both water-soluble and oil-soluble drugs can be administered in emulgel formulations using oil-in-water and water-in-oil emulsions, which can dissolve the drugs and penetrate the skin.[5] When the gel is incorporated into emulsions, the dosage form is called emulgel. In fact, the existence of gel-forming specializers in the water phase turns a classic emulsion into an emulsion-based gel. Dermatological emulgels have preferred properties like thixotropy, grease-free, easy to paint, easy to remove, softened, unstained, water-soluble, longer shelf life, environmentally safe, translucent, and attractive appearance.[6]

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Advantages of Emulgel Dosage Form[7-9]

Hydrophobic Drug Incorporation

Using w/o/w emulsions, hydrophobic drug molecules can be easily integrated into gels. The solubility of lipophilic drugs acts as a barrier, preventing them from being introduced directly into gel bases, as doing so would create problems during drug absorption. Emulgel assists assimilation of less water-soluble drugs into the oily phase and then dispersion of oily globules in the aqua phase leads to the formation of an oil-in-water emulsion. This emulsion may be better at stabilizing drugs and releasing them than simply incorporating them into a gel base. Thus, emulgel has proven that it is a potent drug transport system for hydrophobic drugs and provided them with the benefits of gel formation.

Stable Formulation

In comparison with other topical dosage forms, emulgel is the most stable formulation. Like powder absorbed moisture easily,

creams tend to phase inversion, ointments cause rancidity due to the oily phase.

Superior Entrapment Efficacy

Compared to other novel preparations such as noisome, liposomes struggle with leakage, and insufficient entrapment because of their nano size. In addition, the gel has a three-dimensional polymeric arrangement that allows superior entrapment efficacy.

Low Preparation Cost and Feasibility of Production

Emulgel preparation is simple and requires fewer steps, so it is a more viable production option; the preparation process involves fewer steps, which results in a low preparation cost. Emulgel production does not need any specialized equipment, and the materials used are readily available and relatively inexpensive, which lowers its production costs.

No Thorough Sonication

As an outcome of thorough sonication during the production of novel molecules like liposomes, niosomes the drug may degrade and leak, but emulgels are not susceptible to this problem since no sonication is required.

Controlled Release

Drugs can be released over a longer period of time with emulgels and it is having shorter t1/2.

Patient Compliance

Despite being self-applied and allowing the patients to terminate medication whenever necessary, emulgels improve patient compliance.

Avoid First-pass Metabolism

Prevention against first-pass metabolism by liver emulgels provides the drug at a specific site with greater bioavailability.

Disadvantages of Emulgel Dosage Form[10,11]

Emulgel formulation shows many advantages but also has few disadvantages like,

1. Large particle size drugs (>400 Daltons) are absorbed more slowly through the skin than small particles.
2. During emulsification of an emulgel there may be bubble formation.
3. Some drugs are poorly permeable by the skin.
4. When it deals with dermatitis it shows symptoms like skin irritation.
5. A potential allergic reaction might occur.
6. The epidermis contains an enzyme that can degrade the drug.

Types of Emulgel

1. Macroemulgel
2. Nanoemulgel
3. Microemulgel

Macroemulgel

In general, macroemulsion is the most commonly found emulgel, where its droplet size of emulsion is >400 nm. Thermodynamically, macroemulsion is unstable but surfactants can stabilize them.[12] For example, formulation of itraconazole emulgel was prepared using xanthan gum and guar gum as a gelling agent. Teen 20 and span 20 as surfactant. Paraffin oil was utilized as an oil phase.[13]

Nanoemulgel

When nanoemulsion is absorbed into the gel that term is called nanoemulgel. Nanoemulsion is transparent dispersion of oil phase and water phase in which surfactant and co-surfactant with droplet size <100 nm added they form interfacial film to stabilize the formulation. For example, carvedilol nanoemulgel was formulated by taking oleic acid with isopropyl myristate in a 3:1 ratio which acts as an oil phase. Carbopol 934 was work as a gelling agent. Carbitol and tween 20 were used as co-surfactant and surfactant, respectively.[14]

Microemulgel

Microemulsions are translucent and have thermodynamic stability, the size of their droplets varies between 10 and 100 nm. They do not have coalescence properties. For example, microemulsion-based voriconazole gel was prepared using parker Neem® oil as oil phase and Acrysol™ K-150 as surfactant Carbomer 934P act as gelling agent.[15]

Factors Affecting Topical Assimilation of the Drug[5,16]

Physiological Factors

1. Skin thickness: - From epidermis to hypodermis, skin thickness varies significantly. The epidermis is thick and has about 100–150 μm of thickness. The foot and hand surfaces have a greater rate of skin penetration.
2. Lipid content: - Water can be easily repelled by it. When the horny layer has low lipid weight there is a notable increase in percutaneous penetration
3. The solidity of hair follicles: - About ten times maximum storage capacity than the stratum corneum exists in the hair follicle infundibulum.
4. Blood flow: - More the blood flow more the permeation of drug through the skin.
5. Effect of vehicle: - Gel containing hydroalcoholic provides the best absorption into the skin.
6. Hydration of skin: - Permeation is greater in hydrated skin compared to dry skin. Hydration increases stratum corneum permeability. The fat content of the epidermis does not influence permeability much.
7. Inflammation of skin: - Increasing permeability due to disruption of stratum corneum.
8. Skin temperature: - As skin temperature elevates that increases the level of skin penetration.

Physicochemical Factors

1. Partition coefficient: - The maximum value of log p, increases the better chance of percutaneous absorption by the drug.

2. Molecular weight (<400 Daltons)
3. The state of ionization (mainly unionized drugs get absorbed well)
4. Effect of vehicle: - Gel containing hydroalcoholic provides the best absorption into the skin

Skin Physiology and Function[17-19]

Topical dosage forms are typically applied to the skin; therefore, a basic understanding of the skin's physiological functions is key to developing them. About 1/3 of the circulation through an adult body is carried by the skin, which has a surface area of about 2 m^2 According to studies, every square centimeter of the average human skin contains between 40 and 80 hair follicles and 250–300 sweat ducts respectively. Usually, the pH of the dermis surface ranges between 4 and 5.6, depending on sweat and fat secreted from sebum because they affect the pH of the skin. The skin consists of 4 layers [Figure 1 and Table 1].

Non-viable Epidermis

There are ten to twenty cell layers of stratum corneum covering the body's outermost layer, and it serves as a physical barrier against practically all substances for which skin is exposed. Cells are composed of a plane, platter-like structure between 35 and 45 μm long, 24–35 μm wide, and 0.5–0.20 μm thick, with a surface area between 750 and 1300 μm stacked tightly together in a brick-like fashion. Stratum corneum is composed of lipids (5–15%), phospholipids, glycosphingolipid, cholesterol sulfate, and neutral lipids and proteins (75–85%) made up mostly of keratin.

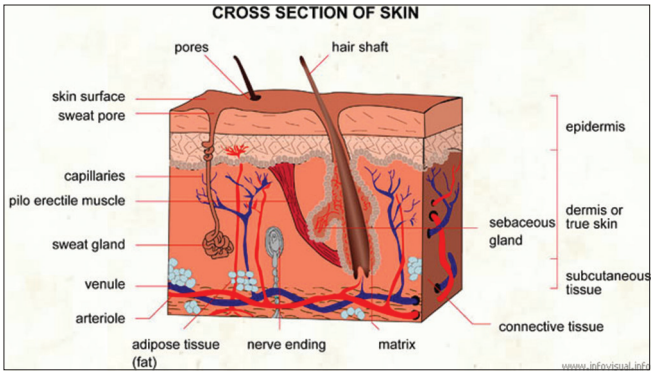

Figure 1: Physiology of skin

Table 1: Categorization of topical dosage form[24]

I. Solid preparation	II. Liquid preparation
1. Topical powder	1. Lotion
2. Poultices	2. Liniment
3. Plaster	3. Paints
	4. Solution
	5. Emulsion
	6. Suspension
III. Miscellaneous preparation	IV. Semisolid preparation
1. TDDS	1. Ointment
2. Tapes and gauzes	2. Creams
3. Rubbing alcohols	3. Pastes
4. Liquid cleaner	4. Gels
5. Topical Aerosol	5. Suppositories

Viable Epidermis

A viable epidermis is located in between the horny layer and dermis and ranges in thickness from 60 to 100 μm. The cells of a viable epidermis share many physicochemical characteristics with other living tissues. Tonofibrils hold cells together. They have a density similar to water, about 90% of their content is water.

Dermis

In the dermis, just beneath the viable epidermis are several different types of fibrins and hardly a few cells look like them histologically in normal tissues. It is composed of a network of loose connective tissue matrix which has protein fibers immersed in an amphorphose ground substance. The dermis can range in thickness from 3000 to 5000 μm.

Subcutaneous Connective Tissue

Although, it is considered a part of the structural connective tissue. Blood and lymph vessels, sweat gland pores, cutaneous nerves, and blood vessels are all contained in the subcutaneous tissues of the hypodermis. The subcutaneous tissues are white, textured, and fibrous connective tissue. According to many researchers, drugs are entering the blood through the skin before they reach the hypodermis. Despite the possibility that fatty tissue could act as a depot for the drugs.

Pathway of the Drug across the Skin

Immediately underneath, the epidermis lies the dermis, and there are numerous vessels that provide the subcutaneous layer. Drugs are penetrated through the skin through three different mechanisms: intercellular, transcellular, and follicular. Pilosebaceous delivery is the next most common method of delivery. Permeation generally occurs through the intercellular matrix, but through a transcellular pathway, highly polar molecules can travel at a faster rate. Drug barriers are maintained by keratinized corneocytes and lipid intercellular cement in the horny layer of normal intact skin.[20] DMSO, surfactants, and propylene glycol can all be used as organic solvents to enhance drug penetration in the skin. As a result of using these organic solvents, the stratum corneum's barrier properties can be changed, such as enhancing solubility, dividing the stratum corneum, and fluidizing its crystalline structure.[21] In the past, creams and gels have been used to treat infections and pain using medication on the skin. As new technology is developed, it can now be used to transport other drugs through the skin. Through systemic routes, drugs can now treat not just skin lesions, but the entire body as well.[22]

Factors Consideration While Choosing a Topically Applied Drug Delivery System[24,11]

1. Vehicle effect: - the occlusive vehicle may facilitate penetration and efficacy of the main drug molecule. It may be cooling, drying, emollient, or protective in nature.
2. Make sure that the preparation matches the type of site (e.g., gel or lotion for the areas where hairs are present).
3. According to the type of lesions, there should be a matching preparation. For example, if you have acute weepy dermatitis, don't use greasy ointments

4. Sensitization or irritation is potential. Ointments and creams without preservatives and emulsifiers are less irritating, whereas gels are more irritating. Ointments do not carry any preservatives and emulsifiers if allergies are a concern.

Formulating Topical Emulgels Presents Some Challenges[17]

1. Assessing the safety of the system by determining whether are they non-toxic, non-comedogenic, and non-irritating.
2. Creating an emulgel with cosmetic appeal.
3. To be suitable for emulgel formulation, it must be low allergic in nature, biologically inert, and physiologically compatible.

Emulsion Based Gel Formulation

Ideal Requirement of Active Pharmaceutical Ingredients[25] [Table 2]

Vehicle

Delivering the drug at the exact location.

Properties

The drug must remain at a sufficient level in the target cell for sufficient time to exert a pharmacological effect. The drug should be released in such a way that it can migrate freely to the site where it is effective.[3]

Aqueous agents

In an emulsion, they act as an aqueous phase. Commonly water and alcohol are used as aqueous agents.[26]

Oils

It is widely accepted that mineral oils are preferred as vehicles for drugs, and they have a property of occlusiveness, as well as their sensory properties for superficially applied emulsions, individually or hard or soft paraffin can be combined with it.[27] There is a huge variety of oils commonly utilized in oral preparation including mineral oil and castor oil that can produce laxative effects, fish liver oil, and various fixed vegetable oil (e.g., Maize oil) as a supplement to nutritional needs.[28] There are a variety of plant oils with different medicinal properties that can be used in emulgel formulation. Hiba *et al*. (2016) carried out one such study work using myrtle oil as part of the oil droplets of an emulgel to treat human skin disease, where this oil phase plays a role of an antimicrobial agent[29] [Table 3].

Gelling polymers

In addition to increasing the consistency of dosage form, they might also be utilized as thickness. A higher concentration of gelling agents will lead to a higher extent of drug release[30-35] [Table 4].

Emulsifiers

To facilitate emulsification during manufacture and to maintain the stability of emulsion during its shelf life, which can range from a few days for a spontaneously prepared emulsion to a month or years for a commercial formulation emulsifying agents need to be included. Polyethylene glycol 40, stearate, stearic acid, sodium stearate, tween 20, span 20 are examples of emulsifiers, when sorbitan monolaurate and polysorbate 20 are used in combination results in greater stability of emulsion than that created by an individual preparation of span or tween.[6,36]

Penetration enhancers

A temporary increase in skin permeability is achieved by these excipients by segregating them into the skin and reacting with skin components[37] [Table 5].

Method of Preparation of Gellified Emulsion[38]

Step 1: Preparation of Gel Using Gelling Polymers

The process described by Williams and Barry[38] was modified slightly to prepare an emulgel. By adding gelling polymers in purified water with continuous stirring at medium speed separately, the gel in the formulation was prepared. In addition, gel pH was adjusted to 6–6.5 by adding triethanolamine.

Table 2: Ideal requirement for active pharmaceutical ingredients

Characteristics of API	*Criteria for acceptance*
Effective dose	<10 mg
Half-life	≤10 h
Molecular weight	500 Daltons or less
Value of Log p	0.8–5
Skin permeability coefficient	$\geq 0.5\times10^{-3}$ cm/h
Skin irritation acceptance	Non-irritating
Polarity	Less
Molecular size	Small
pKa	Higher

Table 3: Examples of oil phases with their quantity

Chemicals	*Quantity (%)*	*Formulation*
Light liquid paraffin	7–7.5	Emulsion and Emulgel
Isopropyl myristate	6–7.5	Emulsion
Isopropyl stearate	6–7.5	Emulsion
Isopropyl palmitate	6–7.5	Emulsion
Propylene glycol	4–5	Gel

Table 4: Gelling polymers with quantity

Gelling polymers	*Quantity (%)*	*Formulation*
Plemulen	0.4	Emulgel
HPMC 2910	2–2.5	Emulgel
Pluronic® F127	2–3	Emulgel
Carbopol 940	1–2	Emulgel
Carbopol 934	1–2	Emulgel
Combination of HPMC and Carbopol.	1.1–1.2	Emulgel

Table 5: Penetration enhancers

Penetration enhancers	*Quantity (%)*	*Formulation*
Menthol	3–5	Emulgel
Linoleic acid	4–5	Gel
Oleic acid	3–4	Gel
Urea	6–8	Gel
Isopropyl myristate	2–5	Gel
Clove oil	3–8	Emulgel

Oil phase

Oil phase was prepared by mixing Span 80 in light liquid paraffin containing the drug dissolved in ethanol for the oil phase.

Aqueous phase

The aqueous phase consisted of dissolved Tween 80 in purified water**.**

Step 2: Formation of Emulsion

The mixer of methyl and propylparaben in propylene glycol was blended with an aqueous phase. Aqueous and oil phases were heated individually at 70–80°C. After this step, the oil phase was continuously added to the aqueous phase on constant stirring until cooled at 25°C to get an emulsion.

Step 3: Addition of Emulsion into Gel

Mix the gel with emulsion in a 1:1 ratio and add glutaraldehyde to get the gellified emulsion.

Evaluation Study[39-44]

Preliminary Test

The Color, homogeneity, consistency, and pH of the emulsion formulations were visually examined. A digital pH meter (DPH 115 PM) was used to measure pH in a 1% aqueous medium of the formulated gellified emulsion.

Fourier Transforms Infrared Spectroscopy

This investigation focused on identifying stable storage conditions and identification of formulation excipients compatible with the solid-state drug.

Viscosity Measurements

Brookfield Engineering Laboratories, USA with spindle 63 was used to determine the rheology, that is, the viscosity of batches of the formulation. The rheology of the formulation batches was measured using the Brookfield viscometer with spindle 63. To determine the viscosity, the formulation was poured into the beaker and let settle down at 25 ± 1°C for 30 min. The viscosity was then measured by lowering the spindle into the middle of the emulgel while making sure not to touch the ground side of the container. After rotating at 48 ± 2 rpm for 10 min, the results were recorded.

Spreadability

To determine the extent of spread, Mutimer *et al*. (1956) suggested a modified apparatus, which can be used in the labs and for the study. The basic structure consists of a block of wood with a pulley at one end. The spreadability of emulgels is determined by measuring "Slip" and "Drag" characteristics. A lowered glass slide is firmly attached to this block. On this ground slide, a portion of the emulsion-based gel sample is placed (about 2 g). The sample is then pressed between the bottom slide and top glass slide with the same dimensions and equipped with the hook. The two slides are placed with a weight of 1 kilogram on top for 5–7 min to eliminate air and between both slides, ensure that there is an even layer of emulgel. An extra emulgel is scraped off from the edges. An 80 g pull is applied to the top plate. Using the string secured to the hook, measure how long it takes for this slide to cover 7.5 cm of distance. A shorter timescale demonstrates better spreadability. The spreading ability of emulgel was calculated using the below formula

$$S = \frac{M.L}{T}$$

where,
S = Spreadability,
M = Weight attached to the upper slide,
L = Length covered by glass slides after applying weight,
T = Separation time between both slides.

Swelling Index

To obtain the swelling index, 1 g of the topical emulgel was deposited on aluminum foil that had pores and then separately placed in a beaker having 10 ml of 0.1 N NaOH. The gel in the beakers was then removed and placed in a moisture-free place for some time. It was later weighed again. The swelling index can be calculated by using the following formula

$$(SW)\ \% = \frac{(Wt. - Wo)}{Wo} \times 100$$

Where,
(SW) % = Percentage of swelling equilibrium,
Wt. = Final weight of swelled Emulgel after time t,
Wo = Initial Emulgel weight at time zero.

Globule Size and Distribution in Emulgel

Globule size and distribution were followed by the Malvern zeta sizer. Agitation is carried out so that the 10 g sample would be uniformly distributed in purified water. As a result of the injection of the sample into the zeta sizer, Estimated the diameter of globules and their distribution.

Study of *in vitro*-Release of the Drug

Studies on drug release from emulgel were done using egg membrane on diffusion cell. This egg membrane was clamped into an empty glass tube of dialysis cells that served as an *in vitro* release device. The egg membrane coated with 1 g amount of emulgel and freshly prepared PBS pH 7.4 solution was filled in the receptor chamber to dissolve the drug. The stirring of that chamber was carried out by a magnetic stirrer. A suitable time interval was selected for sample collection (1 ml aliquots). After dilution to the appropriate level drug content was analyzed using UV-Visible Spectrophotometer. Each time interval the total quantity of drug release was computed using cumulative corrections. On the result of a standard calibration curve, how much drug was released cumulatively across the egg membrane over time was calculated.

Microbiological Assay

In this study, the ditch plate method was used to evaluate semisolid preparations which are mainly suited for the testing fungistatic and

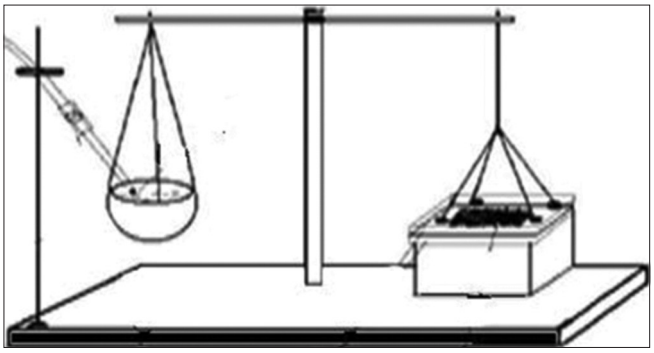

Figure 2: Assembly of bioadhesion strength

bacteriostatic activity. In advance, subouraud's plates were prepared. A cut-out was made in the plates and 3 g of gellified emulsion were applied in the ditch cut. Then, freshly made culture loops are streaked across the agar at a right angle from the ditch to the edge.

Skin Irritation Test[45,48]

An 0.5 g of sample was applied to an area of skin to each site (two sites per rabbit) approximately 1" × 1" (2.54 × 2.54 cm^2) by placing it into a double gauze layer. The rabbit skin was smeared with emulgel. After this step animals were released into their cages. After 24 h of contact, the emulgel formulation was removed. To remove the remaining residue from the test site, tap water was used.

Accelerated Stability Testing[46,49]

Guidelines provided by ICH were followed during the accelerated stability studies. A hot air oven was used at 37 ± 2°, 45 ± 2° and 60 ± 2° to store the preparation for 3 months. An analysis of drug content from the sample was carried out every 2 weeks by UV Visible Spectrophotometer. The change in pH of the gel was also measured every 2 weeks to conduct stability testing.

Ex vivo Bioadhesion Strength Measurement[47-52]

The bioadhesion measurement took place using a modified balance method. The two pans were taken from physical balance. 10 ml beaker was substituted for the right-hand side pan and on the left-hand side pan, a glass slide was hooked. The left-hand side of the assembly was balanced using 20 g of weight. A second glass slide was placed beneath the hanged slide. A section of hairless fresh rat skin was attached to both sides. Approximately, 1 g of emulgel was placed between two rat skin faces on either side. To form a bioadhesive bond light pressure was applied, The right-side beaker was slowly filled with water until the emulgel exuded from the rat face. Mass was determined by converting the quantity of water added. Based on this emulgel bioadhesion strength was calculated in grams [Figure 2].

Conclusion

Following a literature review, it came to the conclusion that emulgels offer the most appropriate and effective deliveries. Despite its nongreasy gel-like property, it also lacks oily bases and gives better dug release compared to other topical treatments. When the emulsion is introduced into a gel as a result dual function control release systems can be created, and problems related to an emulsion such as creaming, separation of phases can be resolved, and its stability is enhanced. A specific drug loaded on an emulgel has shown benefit against some skin disorders, and it may prove useful in the area of dermatology as a delivery system. The hydrophobic drug will be delivered topically in the feature by emulgel. The majority of pharmaceuticals that are useful in treating topical disorders are hydrophobic in nature. Therefore, they can be delivered as emulgel, which is a combined formulation of emulsion and gel. Here are some drugs that have yet to be explored: Tolnaftate, Betamethasone, Dexamethasone.

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